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[54] **HYPOCHOLESTEROLEMIC, ANTIATHEROSCLEROTIC AND HYPOTRIGLYCERIDEMIC MERCAPTOACETYLAMIDE DISULFIDE DERIVATIVES**

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[51] **Int. Cl.**[7] **A61K 31/55**

[52] **U.S. Cl.** **514/214**; 514/824

[58] **Field of Search** 514/214, 824

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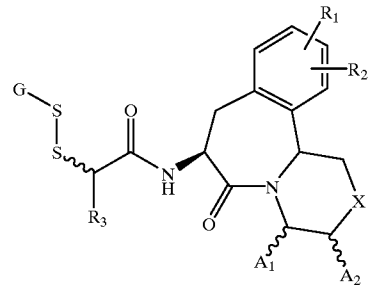
[57] **ABSTRACT**

The present invention relates certain mercaptoacetylamide disulfide derivatives of the formula

Formula (I)



useful in treating patients suffering from hypertriglyceridemia, atherosclerosis and hypercholestrolemia.

17 Claims, No Drawings

HYPOCHOLESTEROLEMIC, ANTIATHEROSCLEROTIC AND HYPOTRIGLYCERIDEMIC MERCAPTOACETYLAMIDE DISULFIDE DERIVATIVES

The present application has an effective international filing date of Feb. 28, 1995 as application Number PCT/US95/02448 which designated the U.S. under 35 USC 371 as a continuation-in-part of application Ser. No. 08/217,471, filed on Mar. 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Coronary heart disease (CHD) remains the leading cause of death in the industrialized countries. Despite recent declines in CHD mortality, CHD is still responsible for more than 500,000 deaths in the U.S. annually. It is estimated that CHD, directly and indirectly, costs the U.S. more than $100 billion a year. The primary cause of CHD is atherosclerosis, a disease characterized by the deposition of lipid (cholesterol and triglycerides) in the arterial vessel wall, resulting in a narrowing of the arterial lumen and ultimately hardening of the arteries.

Atherosclerosis as manifested in its major clinical complication, coronary heart disease (CHD) or ischaemic heart disease, continues to be a major cause of death in industrialized countries. It is now well accepted that atherosclerosis can begin with local injury to the arterial endothelium followed by the penetration of circulatory monocytes into the intima of the arterial wall where they become loaded with lipoprotein derived lipids. At about the same time there seems to be a migration of arterial smooth muscle cells from the medial layer to the intimal layer and their proliferation there along with the deposition of lipid and accumulation of foam cells in the lesion. As the atherosclerotic plaque develops it progressively occludes more and more of the affected blood vessel and can eventually lead to ischaemia, thrombosis or infarction. Therefore, it is desirable to provide methods of inhibiting the progression of atherosclerosis in patients in need thereof.

National Institutes of Health Consensus Development Conference Panel concluded that lowering plasma cholesterol levels (specifically blood levels of low-density lipoprotein cholesterol) will definitely reduce the risk of heart attacks due to CHD. Serum lipoproteins are the carriers for lipids in the circulation. They are classified according to their density; i.e., chylomicrons, very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high-density lipoproteins (HDL). About 50% to 70% of the cholesterol circulating in the blood is carried as LDL. In contrast, about 25% of total cholesterol is found in HDL, while VLDL carries most of the plasma triglycerides and only about 10% to 15% of the total cholesterol.

Chylomicrons are assembled in the intestinal wall from products of lipid digestion and are then transported into the peripheral circulation via the thoracicolymphatic system. In the circulation, they are broken down by lipoprotein lipase (LPL) into free fatty acids and triglycerides which are primarily used by muscles for energy or stored in adipose tissue. The other serum lipoproteins are involved in the

transport of endogenously synthesized lipid. Endogenous lipid transport begins when the liver secretes triglycerides and cholesterol into the plasma as VLDL. The triglycerides of VLDL are cleaved in the capillaries by LPL to IDL and finally LDL. Some of these particles are cleared rapidly by the liver by receptor-mediated endocytosis. The remainder circulate mainly as LDL.

As cells die and cell membranes turn over, cholesterol is continously released into the plasma and becomes HDL. HDL promotes the removal of cholesterol from peripheral cells and facilitates its transport back to the liver.

Arterial wall cholesterol is derived almost exclusively from LDL [Brown and Goldstein, *Ann. Rev. Biochem.* 52, 223 (1983); Miller, *Ann. Rev. Med.* 31, 97 (1980)]. Framingham investigators found the higher the levels of LDL, the higher the risk of devloping CHD [*Am. J. Med.* 80 (Suppl. 2A) 23–32, 1986]. In patients with low levels of LDL, the development of atheroschlerosis is rare [Patton et. al, *Clin. Chem.* 29, 1890 (1983)]. Accordingly, it is desirable to provide a method for reducing plasma cholesterol in patients with hypercholesterolemia or at risk of developing hypercholesterolemia.

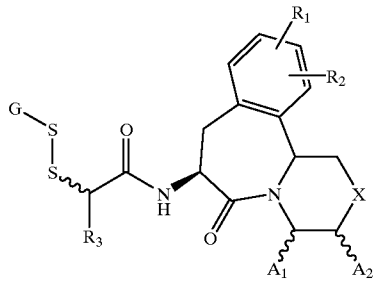
Elevated cholesterol levels are also associated with a number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma. It is desirable to provide a method for reducing plasma cholesterol in patients with, or at risk of developing disease states associated with elevated cholesterol levels.

Hypertriglyceridemia is a condition in which there is an excessive amount of triglyceride (>500 mg/dl) in the plasma. It may play a role in atherogenesis and the development of coronary heart disease [Vega and Grundy, *Adv. Exp. Med.* 243, 311 (1989)]. In addition, severe hypertriglyceridemia (>1000 mg/dl) is associated with chylomicronemia and causes acute pancreatitis [See K. Soergel, ACUTE PANCREATITIS, in *Gastrointestinal Disease* 91, 3rd ed. (Sleisenger, M. H., and Fordtran, J. S., eds.), W. B. Saunders Company, Philadelphia, Pa., 1983, pp. 1462–1485; and See Brown, M. S., and Goldstein, J. L., DRUGS USED IN THE TREATMENT OF HYPERLIPOPROTEINEMIAS, in *Goodman and Gillman's, The Pharmacological Basis of Therapeutics* 34, 7th edition, (Macmillan Publishing Co., New York, 1985, pp. 827–845]. Severe elevations in chylomicrons directly induce pancreatitis, and it can be prevented by triglyceride reduction [U.S. Department of Health and Human Services, NIH Publication No. 89–2925, pp. 74–77, January 1989, "Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults"] It is therefore desirable to provide a method for reducing plasma triglycerides in patients with hypertriglyceridemia.

SUMMARY OF THE INVENTION

The present invention provides a method of treating hypercholesterolemia, atheroscherosis and hypertriglyceridemia in a patient in need thereof comprising administering to said patient an effective hypocholesterolemic, antiatherosclerotic or hypotriglyceridemic amount of a compound of the formula

Formula (I)



wherein

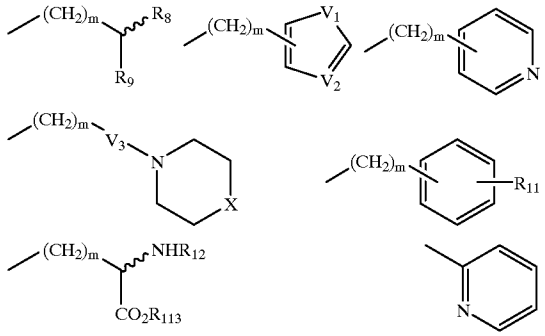
R_1 and R_2 are each independently hydrogen, hydroxy, —OR_4 wherein R_4 is a C_1–C_4 alkyl or an Ar—Y-group wherein Ar is aryl and Y is a C_0–C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

X is —$(CH_2)_n$—, O, S, NR_5, or $NC(O)R_6$ wherein n is an integer 0 or 1, R_5 is hydrogen, a C_1–C_4 alkyl, or an Ar—Y-group, and R_6 is —CF_3, C_1–C_{10} alkyl, or an Ar—Y-group;

A_1 and A_2 are each independently hydrogen or —$COOR_7$ wherein R_7 is hydrogen, —CH_2O—$C(O)C(CH_3)_3$, a C_1–C_4 alkyl, an Ar—Y-group, or diphenylmethyl; with the proviso that where X is —$(CH_2)_n$— and A_1 is hydrogen then A_2 is —$COOR_7$, and where X is —$(CH_2)_n$— and A_1 is —$COOR_7$ then A_2 is hydrogen; and with the further proviso that where X is O, S, NR_5, or $NC(O)R_6$ then A_2 is hydrogen;

R_3 is hydrogen, C_1–C_8 alkyl, —$CH_2OCH_2CH_2OCH_3$ or an Ar—Y-group;

G is a radical chosen from the group;



wherein

m is an integer from 1 to 3;

R_8 is hydrogen, C_1–C_6 alkyl, —$CH_2CH_2S(O)_pCH_3$, or arylalkyl, wherein p is 0, 1, or 2;

R_9 is hydrogen, hydroxy, amino, C_1–C_6 alkyl, N-methylamino, N,N-dimethylamino, —CO_2R_7, or —$OC(O)R_{10}$ wherein R_{10} is hydrogen, C_1–C_6 alkyl, or phenyl;

R_{11} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1–C_4 alkyl, C_1–C_4 alkoxy, or halogen;

R_{12} is hydrogen, C_1–C_6 alkyl, or Ar—Y-group;

R_{13} is hydrogen or C_1–C_4 alkyl;

V_1 is O, S, or NH;

V_2 is N or CH;

V_3 is a direct bond or —C(O)—;

or stereoisomers or pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

As used in this application:

a) the term "C_1–C_6 alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of from one to six carbon atoms and includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, n-pentyl, cyclo-pentyl, n-hexyl, cyclo-hexyl and the like;

b) the term "C_1–C_4 alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of from one to six carbon atoms and includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl;

c) the designation "►" refers to a bond that protrudes forward out of the plane of the page;

d) the designation "▥" refers to a bond that protrudes backward out of the plane of the page;

e) the designation "〰" refers to a bond for which the stereochemistry is not designated;

f) the term "halogen" refers to a fluorine atom, chlorine atom, bromine atom, or iodine atom;

g) the terms "C_1–C_8 alkyl" and "C_1–C_{10} alkyl" refer to saturated straight or branched chain hydrocarbyl radicals of one to eight and one to ten carbon atoms, respectively, including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like;

h) the term "C_1–C_4 alkoxy" refer to a straight or branched alkoxy group containing from 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy, etc;

i) the designation "—C(O)—" refers to a carbonyl group of the formula:

j) the term "Ar—Y-" refers to a radical wherein Ar is an aryl group and Y is a C_0–C_4 alkyl;

k) the term "C_0–C_4 alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of zero to four carbon atoms and includes a bond, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl and the like;

l) the term "Ar" or "aryl group" refers to a phenyl or naphthyl group unsubstituted or substituted with from one to three substituents selected from the group consisting of methylenedioxy, hydroxy, C_1–C_4 alkoxy, fluoro and chloro; specifically included within the scope of the term "arylalkyl" are phenyl, naphthyl, naphthylmethyl, phenylmethyl or benzyl, phenylethyl, p-methoxybenzyl, 3,4-methylenedioxybenzyl, p-fluorobenzyl and p-chlorobenzyl;

m) the term "protected amino" refers to either a —$NHPg_1$ or —NPg_2Pg_3 wherein Pg_1, Pg_2, and Pg_3 are amino protecting groups as described in *Protecting Groups in Organic Synthesis* by T. Greene as is well known and appreciated by those skilled in the art which allow for the formation of disulfides and then are removable to afford compounds of Formula (I) in which R_9 in amino;

n) the term "pharmaceutically acceptable salts" refers to either acid addition salts or to base addition salts.

The expression "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of a compound of Formula (I) or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di-, and tricarboxylic acids. Illustrative of such acids are for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicyclic, 2-phenoxy-benzoic, and sulfonic acids such as p-toluenesulfonic acid, methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form.

The expression "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of a compound of Formula (I) or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, cyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, isopropyldiethylamine, pyridine and picoline.

As used herein, the term "patient" refers to warm-blooded animals or mammals, including rabbits, rodents, monkeys and humans, who are in need of treatment for hypertriglyceridemia atherosclerosis or hypercholesterolemia, such as, for example, in the case of a patient suffering from familial hyperlipidemia. Patients are in need of treatment for hypertriglyceridemia, for example, in the case of a patient suffering from Type IV Hyperlipoproteinemia (indicating elevated VLDL) according to the Fredrickson classification [Fredrickson and Levy, FAMILIAL HYPERLIPOPROTEINEMIA, in *The Metabolic Basis of Inherited Disease,* 3rd ed. (Stanbury, J. B.; Wyngaarden, J. B.; and Fredrickson, D. S.; eds.) McGraw-Hill Book Co., New York, 1972, pp. 545–614].

As is appreciated by one of ordinary skill in the art the compounds of the Formula (I) may exist as stereoisomers. Any reference in this application to one of the compounds of the Formula (I) is meant to encompass either specific stereoisomers or a mixture of stereoisomers. The specific stereoisomers can be prepared by stereospecific synthesis or can be separated and recovered by techniques known in the art, such as chromatography, chromatography on chiral stationary phases, fractional recrystallization of addition salts formed by reagents used for that purpose, as described in *Enantiomers, Racemates, and Resolutions,* J. Jacques, A. Collet, and S. H. Wilen, Wiley (1981).

Examples of compounds encompassed by the present invention include:

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, ethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-hydroxyethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-dimethylaminoethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, benzylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-pyridylmethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-thioacetic acid morpholine carboxamide, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, L-cysteine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, N-acetyl-L-cysteine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, L-cysteine ethyl ester, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-thiopyridine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (R)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-1-(2-methylthioethyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (R)-1-(2-methylthioethyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, ethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-hydroxyethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-dimethylaminoethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, benzylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-pyridylmethylthio, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-

pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-thioacetic acid morpholine carboxamide, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, L-cysteine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, N-acetyl-L-cysteine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, L-cysteine ethyl ester, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-thiopyridine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (R)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-1-(2-methylthioethyl)-2-(thio)-ethylamine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, (R)-1-(2-methylthioethyl)-2-(thio)-ethylamine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, ethylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-hydroxyethylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-dimethylaminoethylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, benzylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-pyridylmethylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-thioacetic acid morpholine carboxamide, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, L-cysteine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, N-acetyl-L-cysteine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, L-cysteine ethyl ester, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-thiopyridine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, (R)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, (S)-1-(2-methylthioethyl)-2-(thio)-ethylamine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, (R)-1-(2-methylthioethyl)-2-(thio)-ethylamine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, ethylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-hydroxyethylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-dimethylaminoethylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, benzylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-pyridylmethylthio, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-thioacetic acid morpholine carboxamide, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, L-cysteine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, N-acetyl-L-cysteine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, L-cysteine ethyl ester, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, 2-thiopyridine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

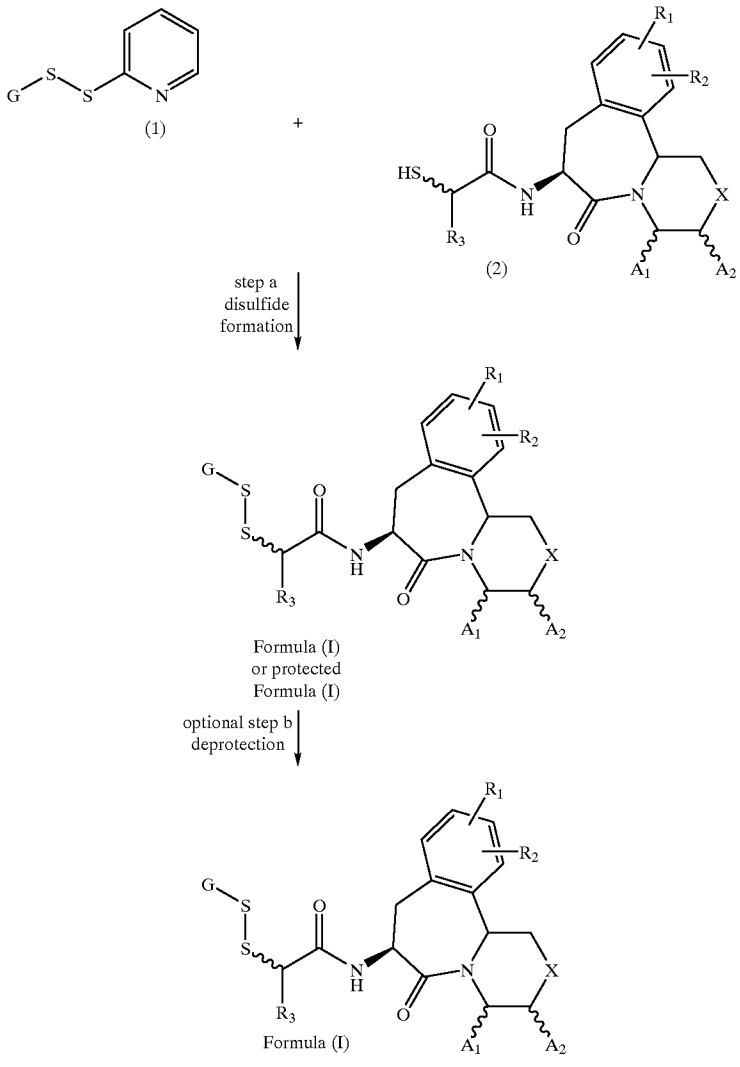
[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, (R)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, (S)-1-(2-methylthioethyl)-2-(thio)-ethylamine, disulfide;

[7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl) amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a] [2]benzazepine, (R)-1-(2-methylthioethyl)-2-(thio)-ethylamine, disulfide.

A general synthetic procedure is set forth in Scheme A for preparing compounds of Formula (I). In Scheme A, all substituents unless otherwise indicated, are as previously defined. Starting materials, reagents, techniques, and procedures used in Scheme A are well known and appreciated by one of ordinary skill in the art.

SCHEME A



The disulfide of structure (1) can be obtained by methods known in the art or by methods known analogously in the art, B. P. Roques et al. *J. Med. Chem.* 33, 2473–2481 (1992). Thiols of structure (2) are known in the art, European Patent Application No. 0 481 522 A1, published Apr. 22, 1992.

In Scheme A, step a, an appropriate disulfide of structure (1) is contacted with an appropriate thiol of structure (2) to give a disulfide of Formula (I) or a protected disulfide of Formula (I). An appropriate disulfide of structure (1) is one in which G is as desired in the final product of Formula (I) or gives rise upon deprotection to G as is desired in the final product of Formula (I). An appropriate thiol of the structure (2) is one in which R_1, R_2, R_3, A_1, A_2, and X are as desired in the final product of Formula (I) or give rise after deprotection to R_1, R_2, R_3, A_1, A_2, and X as desired in the final product of Formula (I).

For example, an appropriate disulfide of structure (1) is contacted with an appropriate thiol of structure (2). The reaction is carried out in a suitable solvent, such as ethanol, methanol, dichloromethane, or mixtures of ethanol or methanol and dichloromethane. The solvent is degassed by passing a stream of nitrogen gas through it for 15 minutes before the reaction is carried out. The reaction is carried out using from 1.0 to 4.0 molar equivalents of an appropriate compound of structure (1). The reaction is carried out at temperatures of from 0° C. to the refluxing temperature of the solvent, with a temperature of 10° C. to 30° C. being preferred. The reaction generally requires from 1 to 48 hours. The product can be isolated by techniques well known in the art, such as extraction, evaporation, and precipitation. The product can be purified by chromatography and recrystallization.

In Scheme A, optional step b, a protected disulfide of Formula (I) is deprotected to give a disulfide of Formula (I).

The selection, use, and removal of protecting groups and the removal of protecting groups in a sequential manner utilizing suitable protecting groups such as those described in *Protecting Groups in Organic Synthesis* by T. Greene is well known and appreciated by those skilled in the art. The removal of protecting groups or the removal of protecting groups in a sequential manner as required gives disulfides of Formula (I).

The following examples present typical syntheses as described in Scheme A. These examples are understood to be illustrative only and are not intended to limit the scope of the invention in any way. As used in the following examples,

the following terms have the meanings indicated: "g" refers to grams, "mmol" refers to millimoles, "mL" refers to milliliters, "°C." refers to degrees Celsius, "R_f" refers to retention factor, "mp" refers to melting point, "dec" refers to decomposition, "M" refers to molar, and "TLC" refers to thin layer chromatography.

EXAMPLE 1

[7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, Disulfide

Scheme A, step a:

Combine [7α(R*),12bβ]-7-[(S)-(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine (0.284 g, 0.72 mmol) and (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, 2-thiopyridine, disulfide (0.297 g, 0.867 mmol) in degassed ethanol (7 mL). Stir for 18 hours. Evaporate in vacuo. Chromatograph on silica gel eluting sequentially with 20% ethyl acetate/hexane and then 33% ethyl acetate/hexane to give the title compound as a foam.

EXAMPLE 2

[7α(R*), 12bβ]-7-[(S)-(1-Oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, Disulfide

Scheme A, step a:

Combine (7α(R*),12bβ]-7-[(S)-(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3, 4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine (0.480 g, 1.20 mmol) and (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, 2-thiopyridine, disulfide (0.500 g, 1.46 mmol) in degassed ethanol (10 mL). Stir for 20 hours. Evaporate in vacuo. Chromatograph of silica gel eluting sequentially with 20% ethyl acetate/hexane and then 33% ethyl acetate/hexane to give the title compound as a foam.

EXAMPLE 3

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, Disulfide

Scheme A, step a:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid (0.531 g, 1.21 mmol) and (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, 2-thiopyridine, disulfide (0.415 g, 1.21 mmol) in degassed ethanol (10 mL). Stir for 18 hours. Evaporate in vacuo. Chromatograph of silica gel eluting with 25% ethyl acetate/hexane to give the title compound.

EXAMPLE 4

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, Diphenylmethyl Ester, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, Disulfide

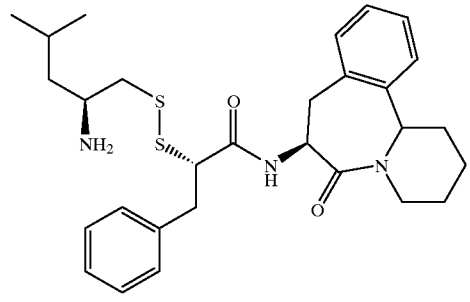
Scheme A, step a:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (0.500 g, 0.827 mmol) and (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, 2-thiopyridine, disulfide (0.340 g, 0.992 mmol) in degassed ethanol (10 mL). Stir for 18 hours. Evaporate in vacuo. Chromatograph of silica gel eluting sequentially with 25% ethyl acetate/hexane and 33% ethyl acetate/hexane to give the title compound as a foam.

EXAMPLE 5

[7α(R*), 12bβ]-7-[(S)-(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, Disulfide Trifluoroacetic Acid Salt

Scheme A, optional step b:

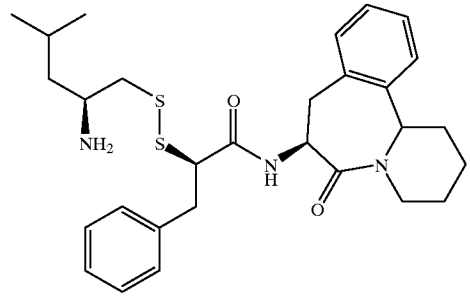


Combine [7α(R*), 12bβ]-7-[(S)-(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide and trifluoroacetic acid (1 mL) in dichloromethane (5 mL). Stir for 3 hours and evaporate in vacuo. Repeatedly, add carbon tetrachloride and evaporate in vacuo to remove residual trifluoroacetic acid. Evaporation in vacuo from hexane/dichloromethane gives the title compound as a solid.

EXAMPLE 6

[7α(R*), 12bβ]-7-[(S)-(1-Oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)ethylamine, Disulfide Trifluoroacetic Acid Salt

Scheme A, optional step b:



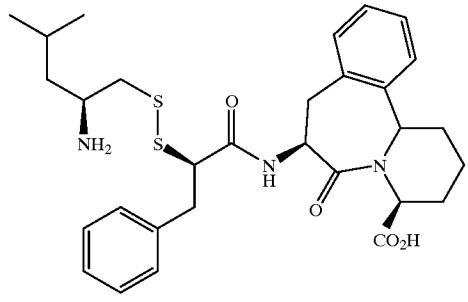
Combine [7α(R*), 12bβ]-7-[(S)-(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-

pyrido[2,1-a][2]benzazepine, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide (0.61 g, 0.975 mmol) and trifluoroacetic acid (2 mL) in dichloromethane (10 mL). Stir for 3 hours and evaporate in vacuo. Repeatedly, add carbon tetrachloride and evaporate in vacuo to remove residual trifluoroacetic acid. Evaporation in vacuo from hexane/dichloromethane gives the title compound as a solid. Mass spectrum CI/CH_4 $[M+H]^+$ 526.

EXAMPLE 7

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, Disulfide Trifluoroacetic Acid Salt

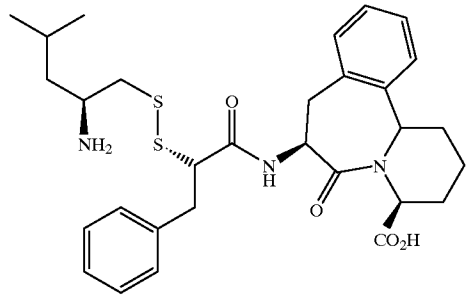
Scheme A, optional step b:



Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide (0.730 g, 1.09 mmol) and trifluoroacetic acid (2 mL) in dichloromethane (5 mL). Stir for 4 hours and evaporate in vacuo. Dry in vacuo at 40° C. to give the title compound as a foam. Mass spectrum CI/CH_4 $[M+H]^+$ 570.

EXAMPLE 8

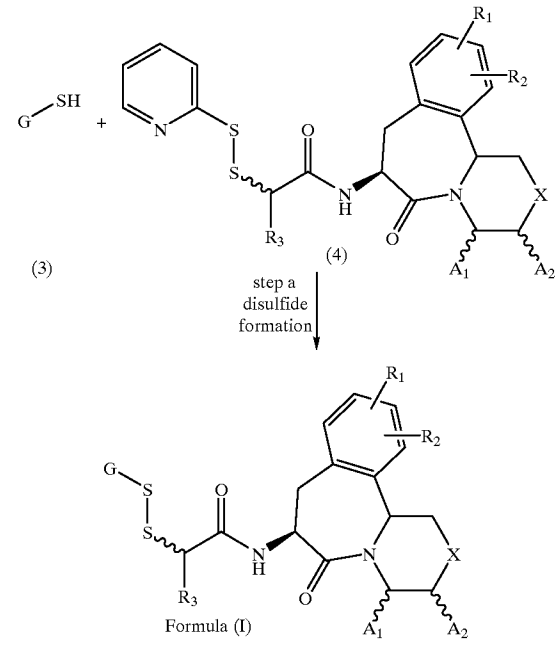
[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, Disulfide Trifluoroacetic Acid Salt



Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, (S)-N-(t-butoxycarbonyl)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide (0.486 g, 0.77 mmol) anisole (7.7 mmol) and trifluoroacetic acid (1.4 mL) in dichloromethane (7 mL). Stir for 3 hours and evaporate in vacuo to obtain a residue. Triturate the residue with hexane to give a solid, filter and dry in vacuo to give the title compound as a solid. Mass spectrum CI/CH_4 $[M+H]^+$ 570.

An alternate general synthetic procedure is set forth in Scheme B for preparing compounds of Formula (I). In Scheme B, all substituents unless otherwise indicated, are as previously defined. Starting materials, reagents, techniques, and procedures used in Scheme B are well known and appreciated by one of ordinary skill in the art.

SCHEME B



In Scheme B, step a, an appropriate thiol of structure (3) is contacted with an appropriate disulfide of structure (4) to give a disulfide of Formula (I) or a protected disulfide of Formula (I) by the method taught above in Scheme A, step a. An appropriate thiol of structure (3) is one in which G is as desired in the final product of Formula (I) or gives rise after deprotection to G as desired in the final product of Formula (I). An appropriate disulfide of the structure (6) is one in which R_1, R_2, R_3, A_1, A_2, and X are as desired in the final product of Formula (I) or give rise after deprotection to R_1, R_2, R_3, A_1, A_2, and X as desired in the final product of Formula (I). An appropriate compound of structure (6) can be prepared by methods known analogously in the art, B. P. Roques et al, *J. Med. Chem.* 33, 2473–2481 (1992), from compounds of structure (2) which are known in the art European Patent Application No. 0 481 522 A1, published Apr. 22, 1992.

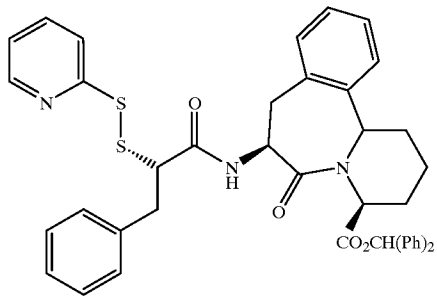
In Scheme B, optional step b, a protected disulfide of Formula (I) is deprotected to give a disulfide of Formula (I) as taught in Scheme A, optional step b, above.

The following examples present typical syntheses as described in Scheme B. These examples are understood to be illustrative only and are not intended to limit the scope of the invention in any way. As used in the following examples, the following terms have the meanings indicated: "g" refers to grams, "mmol" refers to millimoles, "mL" refers to milliliters, "°C." refers to degrees Celsius, "R_f" refers to retention factor, "mp" refers to melting point, "dec" refers to decomposition, "M" refers to molar, and "TLC" refers to thin layer chromatography.

EXAMPLE 9

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, Diphenylmethyl Ester, 2-thiopyridine, Disulfide

Scheme A, step a:



Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (0.424 g, 4.0 mmol) and 2,2'-dithiodipyridine (3.5 g, 16.0 mmol) is degassed ethanol (24 mL) and dichloromethane (6 mL). Stir under an inert atmosphere at ambient temperature for 20 hours. Evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting sequentially with 25% ethyl acetate/hexane and then 40% ethyl acetate/hexane to give the title compound.

EXAMPLE 10

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, Diphenylmethyl Ester, N-(t-butoxycarbonyl)-L-cysteine Ethyl Ester, Disulfide

Scheme B, step a:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, 2-thiopyridine, disulfide (1.00 g, 1.4 mmol) and N-(t-butoxycarbonyl)-L-cysteine ethyl ester (0.49 g, 2.0 mmol) in degassed ethanol/dichloromethane (10 mL)/(2 mL). Stir for 18 hours. Evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting sequentially with 28% ethyl acetate/hexane and then 40% ethyl acetate/hexane to give the title compound.

EXAMPLE 11

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, Diphenylmethyl Ester, Benzylthio, Disulfide

Scheme B, step a:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, 2-thiopyridine, disulfide (1.00 g, 1.4 mmol) and benzylthiol (0.2 mL, 1.7 mmol) in degassed ethanol/dichloromethane (15 mL)/(3 mL). Stir for 18 hours. Add benzylthiol (0.15 mL, 1.35 mmol) and stir for 24 hours. Evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting sequentially with 25% ethyl acetate/hexane and then 30% ethyl acetate/hexane to give the title compound as a solid.

EXAMPLE 12

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic Acid, Diphenylmethyl Ester, Ethylthio, Disulfide

Scheme B, step a:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido]2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, 2-thiopyridine, disulfide (1.20 g, 1.68 mmol) and ethylthiol (0.2 mL, 2.7 mmol) in degassed ethanol/dichloromethane (15 mL)/(3 mL). Stir for 18 hours. Add ethylthiol (0.20 mL, 2.7 mmol) and stir for 24 hours. Evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting 30% ethyl acetate/hexane to give the title compound as a solid.

EXAMPLE 13

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic Acid, Diphenylmethyl Ester, 2-hydroxyethylthio, Disulfide

Scheme B, step a:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, 2-thiopyridine, disulfide (1.10 g, 1.54 mmol) and 2-hydroxyethylthiol (0.2 mL, 2.85 mmol) in degassed ethanol/dichloromethane (15 mL)/(3 mL). Stir for 18 hours. Dilute with dichloromethane and extract with saturated sodium chloride solution. Dry the organic layer over $MgSO_4$, filter, and concentrate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting sequentially with 30% ethyl acetate/hexane and then 50% ethyl acetate/hexane to give the title compound.

EXAMPLE 14

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic Acid, Diphenylmethyl Ester, 2-pyridylmethylthio, Disulfide

Scheme B, step a:

Combine (4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, 2-thiopyridine, disulfide (1.00 g, 1.40 mmol) and pyridylmethylthiol (0.26 g, 2.10 mmol) in degassed ethanol/dichloromethane (10 mL)/(2 mL). Stir for 18 hours. Concentrate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting sequentially with 30% ethyl acetate/hexane and then 50% ethyl acetate/hexane to give the title compound.

EXAMPLE 15

2-Thiolacetic Acid Morpholine Carboxamide

Preparation of starting material for Scheme B, step a:

Combine chloroacetyl chloride (2.00 mL, 25.0 mmol) and N-methylmorpholine (2.76 mL, 25.0 mmol) in dichloromethane (100 mL). Cool in an ice-bath. Add morpholine (2.19 mL, 25.0 mmol) and stir in the ice-bath for 1 hour. Warm to ambient temperature and stir for 1 hour. Extract with cold aqueous 5% sulfuric acid solution, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution. Dry the organic layer over Na_2SO_4, filter, and evaporate in vacuo to obtain chloroacetic acid morpholine carboxamide.

Combine chloroacetic acid morpholine carboxamide prepared above (2.88 g, 17.6 mmol) and thiolacetic acid (1.40 mL, 20.0 mmol) in degassed dimethylformamide (10 mL). Slowly add cesium carbonate (3.26 g, 10.0 mmol) providing cooling as needed to keep the temperature of the reaction mixture below 40° C. Stir at ambient temperature for 16 hours. Partition the reaction mixture between water and ethyl acetate. Dry the organic layer over Na_2SO_4, filter, and evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting sequentially with 40% ethyl acetate/hexane and then 66% ethyl acetate/hexane to give 2-acetylthioacetic acid morpholine carboxamide.

Combine 2-acetylthioacetic acid morpholine carboxamide obtained above (2.50 g, 12.0 mmol) and degassed methanol (50 mL). Cool in an ice-bath. Add lithium hydroxide hydrate (1.0 g, 24.0 mmol). Stir for 3 hours. Acidify the reaction mixture to pH=1 with 6 M hydrochloric acid solution. Partition the reaction mixture between water and dichloromethane. Extract the organic layer with saturated aqueous ammonium chloride solution. Dry the organic layer over Na_2SO_4, filter, and evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting with ethyl acetate to give the title compound.

EXAMPLE 16

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic Acid, Diphenylmethyl Ester, 2-thioacetic Acid Morpholine Carboxamide, Disulfide

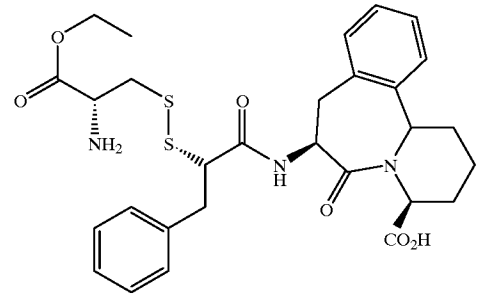
Scheme B, step a:

Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, 2-thiopyridine, disulfide (1.00 g, 1.40 mmol) and 2-thiolacetic acid morpholine carboxamide (0.32 g, 2.0 mmol) in degassed ethanol/dichloromethane (10 mL)/(2 mL). Stir for 16 hours. Concentrate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting with 50% ethyl acetate/dichloromethane to give the title compound.

EXAMPLE 17

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic Acid, L-cysteine Ethyl Ester, Disulfide Trifluoroacetic Acid Salt

Scheme B, optional step b:

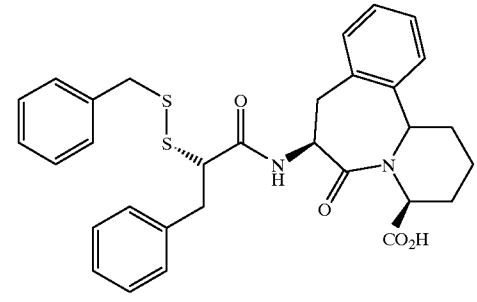


Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, N-(t-butoxycarbonyl)-L-cysteine ethyl ester, disulfide (1.12 g, 1.31 mmol) anisole (1.4 mL, 13.0 mmol) and dichloromethane (15 mL). Cool in an ice-bath. add trifluoroacetic acid (3 mL). Stir for 2 hours in the ice-bath and thee warm to ambient temperature and stir an additional 2 hours. Evaporate in vacuo to obtain a residue. Add carbon tetrachloride to the residue and evaporate in vacuo to obtain a residue. Triturate with hexane, filter and dry in vacuo to give the title compound as a solid. Mass spectrum CI/CH_4 $[M+H]^+$ 586.

EXAMPLE 18

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic Acid, Benzylthio, Disulfide

Scheme B, optional step b:



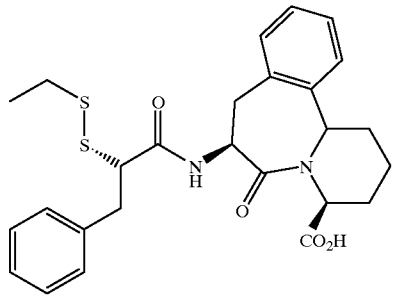
Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, benzylthio, disulfide (0.74 g, 1.02 mmol) anisole (1.1 mL, 10.0 mmol) and dichloromethane (10 mL). Cool in an ice-bath. Add trifluoroacetic acid (2.0 mL). Stir for 2.5 hours in the ice-bath. Evaporate in vacuo to obtain a residue. Dissolve the residue in diethyl ether and extract with 1M hydrochloric acid solution. Extract the aqueous layer with dichloromethane. Combine the organic layers, dry over $MgSO_4$, filter and concentrate in vacuo to obtain a residue.

Chromatograph the residue on silica gel eluting with 50% ethyl acetate/hexane containing 1% acetic acid to give the title compound as a solid. Mass spectrum CI/CH_4 $[M+H]^+$ 561.

EXAMPLE 19

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic Acid, Ethylthio, Disulfide

Scheme B, optional step b:

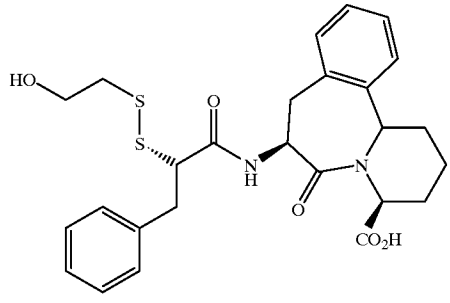


Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, ethylthio, disulfide (0.95 g, 1.43 mmol) anisole (1.1 mL, 10.0 mmol) and dichloromethane (14 mL). Cool in an ice-bath. Add trifluoroacetic acid (2.0 mL). Stir for 2.5 hours in the ice-bath. Evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting with 50% ethyl acetate/hexane containing 1% acetic acid to give the title compound as a solid. Mass spectrum CI/CH_4 $[M+H]^+$ 499.

EXAMPLE 20

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido(2,1-a][2]benzazepine-4-carboxylic Acid, 2-hydroxyethylthio, Disulfide

Scheme B, optional step b:

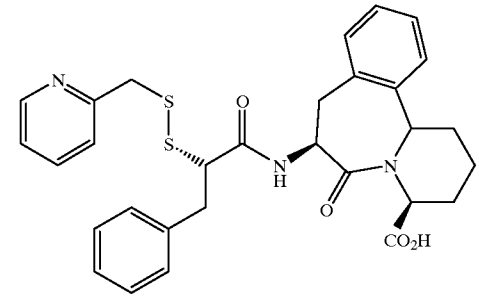


Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, 2-hydroxyethylthio, disulfide (0.63 g, 0.925 mmol) anisole (1.1 mL, 10.0 mmol) and dichloromethane (10 mL). Cool in an ice-bath. Add trifluoroacetic acid (2.0 mL). Stir for 2.5 hours in the ice-bath. Evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting sequentially with with 50% ethyl acetate/hexane containing 1% acetic acid and then with 50% ethyl acetate/hexane containing 5% acetic acid to give the title compound as a solid. Mass spectrum CI/CH_4 $[M+H]^+$ 515.

EXAMPLE 21

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic Acid, 2-pyridylmethylthio, Disulfide

Scheme B, optional step b:

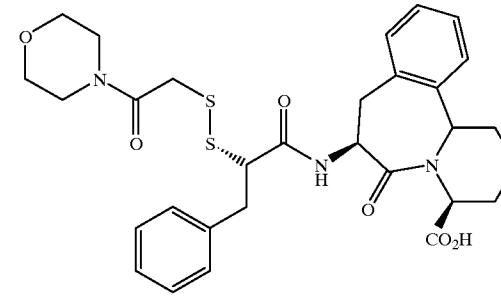


Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, 2-pyridylmethylthio, disulfide (0.387 g, 0.53 mmol) anisole (0.75 mL, 6.9 mmol) and dichloromethane (15 mL). Cool in an ice-bath. Add trifluoroacetic acid (1.4 mL). Stir for 3 hours in the ice-bath. Evaporate in vacuo to obtain a residue. Add carbon tetrachloride to the residue and evaporate in vacuo to obtain a residue. Triturate with hexane, filter and dry in vacuo to give the title compound as a solid. Mass spectrum FAB $[M+H]^+$ 562.

EXAMPLE 22

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic Acid, 2-thioacetic Acid Morpholine Carboxamide, Disulfide

Scheme B, optional step b:



Combine [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester, 2-thioacetic acid morpholine carboxamide (0.52 g, 0.68 mmol) anisole (0.75 mL, 6.9 mmol) and dichloromethane (7.5 mL). Cool in an ice-bath. Add trifluoroacetic acid (2.0 mL). Stir for 2 hours in the ice-bath. Evaporate in vacuo to obtain a residue. Chromatograph the residue on silica gel eluting sequentially with 50% ethyl acetate/

hexane, 70% ethyl acetate/hexane containing 10% acetic acid, and then with 75% ethyl acetate/hexane containing 9% acetic acid to give the title compound as a solid. Mass spectrum FAB $[M+H]^+$ 598.

Hypercholesterolemia is a disease state characterized by levels of serum cholesterol or of LDL cholesterol which are elevated by a clinically significant amount over that considered normal by those of ordinary skill in the art. The identification of those patients who are in need of treatment for hypercholesterolemia is well within the ability and knowledge of one skilled in the art. For example, individuals who have serum cholesterol levels or LDL cholesterol levels, as determined by clinical laboratory tests, which are substantially and chronically elevated over that considered normal by those of ordinary skill in the art, are patients in need of treatment for hypercholesterolemia. By way of further example, individuals who are at risk of developing hypercholesterolemia can also be patients in need of treatment for hypercholesterolemia. A clinician skilled in the art can readily identify, by the use of clinical tests, physical examination and medical/family history, those patients who are suffering from hypercholesterolemia and those who are at risk of developing hypercholesterolemia and thus readily determine if an individual is a patient in need of treatment for hypercholesterolemia.

An effective hypocholesterolemic amount of a compound of Formula (I) is an amount which is effective in reducing serum cholesterol levels or LDL cholesterol levels in a patient in need thereof. As such, successful treatment of a patient for hypercholesterolemia is understood to include reducing a patient's serum cholesterol or LDL cholesterol levels. Successful treatment for hypercholesterolemia is also understood to include prophylaxis in preventing clinically significant elevations in serum cholesterol or in LDL cholesterol levels in a patient who is at risk of the development of hypercholesterolemia.

Atherosclerosis is a disease state characterized by the development and growth of atherosclerotic lesions or plaque. The identification of those patients who are in need of treatment for atherosclerosis is well within the ability and knowledge of one skilled in the art. For example, individuals who are either suffering from clinically significant atherosclerosis or who are at risk of developing clinically significant atherosclerosis are patients in need of treatment for atherosclerosis. A clinician skilled in the art can readily determine, by the use of clinical tests, physical examination and medical/family history, if an individual is a patient in need of treatment for atherosclerosis.

An effective antiatherosclerotic amount of a compound of Formula (I) is an amount which is effective in inhibiting development or growth of atherosclerosis in a patient in need thereof. As such, successful treatment of a patient for atherosclerosis is understood to include effectively slowing, interrupting, arresting, or stopping atherosclerotic lesion or plaque development or growth and does not necessarily indicate a total elimination of the atherosclerosis. It is further understood and appreciated by those skilled in the art that successful treatment for atherosclerosis can include prophylaxis in preventing atherosclerotic lesion or plaque formation.

An effective antiatherosclerotic or hypocholesterolemic dose can be readily determined by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to: the species of patient; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

An effective antiatherosclerotic or hypocholesterolemic amount of a compound of Formula (I) will generally vary from about 1 milligram per kilogram of body weight per day (mg/kg/day) to about 1000 milligrams per kilogram of body weight per day (1 gm/kg/day). A daily dose of from about 2 mg/kg to about 200 mg/kg is preferred.

In effecting treatment of a patient, a compound of Formula (I) can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, the compound can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

Compounds of Formula (I) can be administered in the form of pharmaceutical compositions or medicaments which are made by combining the compound of Formula (I) with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

Hypertriglyceridemia is a disease state characterized by levels of plasma triglycerides which are elevated by a clinically significant amount over that considered normal by those of ordinary skill in the art. The identification of those patients who are in need of treatment for hypertriglyceridemia is well within the ability and knowledge of one skilled in the art. For example, individuals who have plasma triglyceride levels, as determined by clinical laboratory tests, which are substantially and chronically elevated over that considered normal by those of ordinary skill in the art, are patients in need of treatment for hypertriglyceridemia. By way of further example, individuals who are at risk of developing hypertriglyceridemia can also represent patients in need of treatment for hypertriglyceridemia. A clinician skilled in the art can readily identify, by the use of clinical tests, physical examination and medical/family history, those patients who are suffering from hypertriglyceridemia and those who are at risk of developing hypertriglyceridemia and thus readily determine if an individual is a patient in need of treatment for hypertriglyceridemia.

An effective hypotriglyceridemic amount of a compound of Formula (I) is an amount which is effective in reducing plasma triglyceride levels in a patient in need thereof. As such, successful treatment of a patient for hypertriglyceridemia is understood to include reducing a patient's plasma triglyceride levels. Successful treatment for hypertriglyceridemia is also understood to include prophylaxis in preventing clinically significant elevations in plasma triglyceride levels in a patient who is at risk of the development of hypertriglyceridemia.

An effective hypotriglyceridemic dose can be readily determined by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to: the species of patient; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular

compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

An effective hypotriglyceridemic amount of a compound of Formula (I) will generally vary from about 1 milligram per kilogram of body weight per day (mg/kg/day) to about 1000 milligrams per kilogram of body weight per day (gm/kg/day). A daily dose of from about 2 mg/kg to about 200 mg/kg is preferred.

In effecting treatment of a patient, a compound of Formula (I) can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, the compound can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

A compound of Formula (I) can be administered in the form of pharmaceutical compositions or medicaments which are made by combining a compound of Formula (I) with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solution, suspensions, or the like.

The pharmaceutical compositions may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, a compound Formula (I) may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of Formula (I), the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the active ingredient present in compositions is such that a unit dosage form suitable for administration will be obtained.

The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants, such as magnesium stearate or Sterotex; glidants, such as colloidal silicon dioxide; and sweetening agents, such as sucrose or saccharin may be added or flavoring agents, such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral administration, a compound of Formula (I) may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the active ingredient present in such compositions is such that a suitable dosage will be obtained.

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of toxicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

The following example illustrates the utility of the mercaptoacetylamide derivatives of the present invention as hypocholesterolemic, antiatherosclerotic and hypocholesterolemic agents. This example is understood to be illustrative only and is not intended to limit the scope of the present invention in any way.

EXAMPLE 23

Rabbit Test for Hypocholesterolemic, Antiatherosclerotic and Hypotriglyceridemic Activities

Feed rabbits a high cholesterol (1%) diet for eight weeks, supplementing the diets of certain rabbits with the agent of interest. At the end of eight weeks, sacrifice the rabbits, collect the serum and determine cholesterol and triglyceride levels by standard methods [*Hypertension* 15:327–331, 1990].

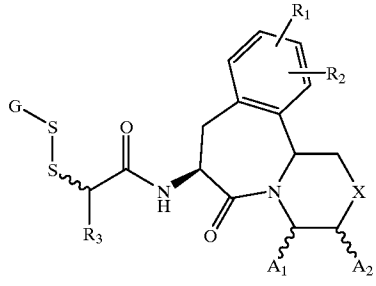
Dissect the aorta of each rabbit from the ascending arch to the iliac bifurcation, clean and prepare for staining with Sudan IV to determine areas of atherosclerotic lesion with the use of image analysis.

Make statistical comparisons between the control and drug-treated groups to determine the activity of the agent of interest.

What is claimed is:

1. A method of lowering total serum cholesterol in a patient in need thereof comprising administering to said patient a therapeutically effective hypocholesterolemic amount of a compound of the Formula

Formula (I)



wherein

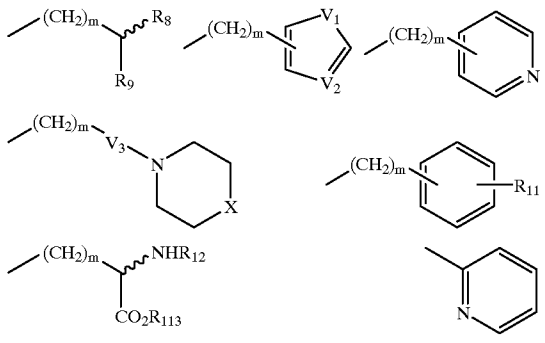
R_1 and R_2 are each independently hydrogen, hydroxy, —OR_4 wherein R_4 is a C_1–C_4 alkyl or an Ar—Y-group wherein Ar is aryl and Y is a C_0–C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

X is —$(CH_2)_n$—, O, S, NR_5, or $NC(O)R_6$ wherein n is an integer 0 or 1, R_5 is hydrogen, a C_1–C_4 alkyl, or an Ar—Y-group, and R_6 is —CF_3, C_1–C_{10} alkyl, or an Ar—Y-group;

A_1 and A_2 are each independently hydrogen or —$COOR_7$ wherein R_7 is hydrogen, —CH_2O—$C(O)C(CH_3)_3$, a C_1–C_4 alkyl, an Ar—Y-group, or diphenylmethyl; with the proviso that where X is —$(CH_2)_n$— and A_1 is hydrogen then A_2 is —$COOR_7$, and where X is —$(CH_2)_n$— and A_1 is —$COOR_7$ then A_2 is hydrogen; and with the further proviso that where X is O, S, NR_5, or $NC(O)R_6$ then A_2 is hydrogen;

R_3 is hydrogen, C_1–C_8 alkyl, —$CH_2OCH_2CH_2OCH_3$ or an Ar—Y-group;

G is a radical chosen from the group;



wherein

m is an integer from 1 to 3;

R_8 is hydrogen, C_1–C_6 alkyl, —$CH_2CH_2S(O)_pCH_3$, or arylalkyl, wherein p is 0, 1, or 2;

R_9 is hydrogen, hydroxy, amino, C_1–C_6 alkyl, N-methylamino, N,N-dimethylamino, —CO_2R_7, or —$OC(O)R_{10}$ wherein R_{10} is hydrogen, C_1–C_6 alkyl, or phenyl;

R_{11} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1–C_4 alkyl, C_1–C_4 alkoxy, or halogen;

R_{12} is hydrogen, C_1–C_6 alkyl, or Ar—Y-group;

R_{13} is hydrogen or C_1–C_4 alkyl;

V_1 is O, S, or NH;

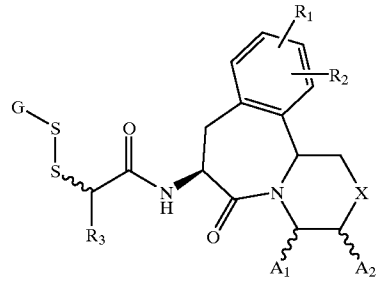
V_2 is N or CH;

V_3 is a direct bond or —C(O)—;

or stereoisomers or pharmaceutically acceptable salts thereof.

2. A method of treating a patient for hypercholesterolemia comprising administering to said patient a therapeutically effective hypocholesterolemic amount of a compound of the Formula

Formula (I)



wherein

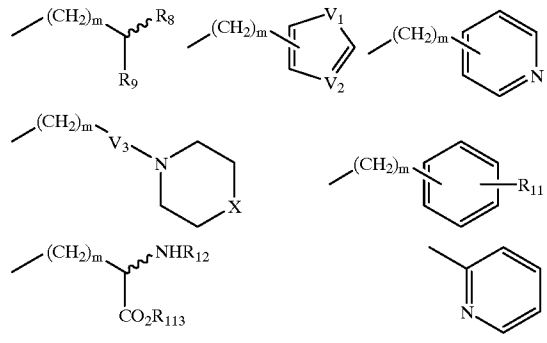
R_1 and R_2 are each independently hydrogen, hydroxy, —OR_4 wherein R_4 is a C_1–C_4 alkyl or an Ar—Y-group wherein Ar is aryl and Y is a C_0–C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

X is —$(CH_2)_n$—, O, S, NR_5, or $NC(O)R_6$ wherein n is an integer 0 or 1, R_5 is hydrogen, a C_1–C_4 alkyl, or an Ar—Y-group, and R_6 is —CF_3, C_1–C_{10} alkyl, or an Ar—Y-group;

A_1 and A_2 are each independently hydrogen or —$COOR_7$ wherein R_7 is hydrogen, —CH_2O—$C(O)C(CH_3)_3$, a C_1–C_4 alkyl, an Ar—Y-group, or diphenylmethyl; with the proviso that where X is —$(CH_2)_n$— and A_1 is hydrogen then A_2 is —$COOR_7$, and where X is —$(CH_2)_n$— and A_1 is —$COOR_7$ then A_2 is hydrogen; and with the further proviso that where X is O, S, NR_5, or $NC(O)R_6$ then A_2 is hydrogen;

R_3 is hydrogen, C_1–C_8 alkyl, —$CH_2OCH_2CH_2OCH_3$ or an Ar—Y-group;

G is a radical chosen from the group;



wherein

m is an integer from 1 to 3;

R_8 is hydrogen, C_1–C_6 alkyl, —$CH_2CH_2S(O)_pCH_3$, or arylalkyl, wherein p is 0, 1, or 2;

R_9 is hydrogen, hydroxy, amino, C_1–C_6 alkyl, N-methylamino, N,N-dimethylamino, —CO_2R_7, or —$OC(O)R_{10}$ wherein R_{10} is hydrogen, C_1–C_6 alkyl, or phenyl;

R_{11} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1–C_4 alkyl, C_1–C_4 alkoxy, or halogen;

R_{12} is hydrogen, C_1–C_6 alkyl, or Ar—Y-group;

R_{13} is hydrogen or C_1–C_4 alkyl;

V_1 is O, S, or NH;

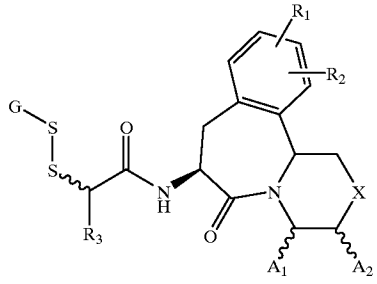
V_2 is N or CH;

V_3 is a direct bond or —C(O)—;

or stereoisomers or pharmaceutically acceptable salts thereof.

3. A method of lowering plasma triglycerides in a patient in need thereof comprising administering to said patient a therapeutically effective hypotriglyceridemic amount of a compound of the Formula

Formula (I)



wherein

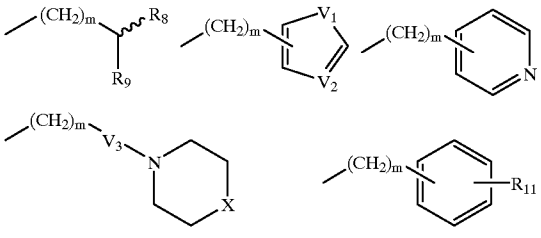
R_1 and R_2 are each independently hydrogen, hydroxy, —OR_4 wherein R_4 is a C_1–C_4 alkyl or an Ar—Y-group wherein Ar is aryl and Y is a C_0–C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

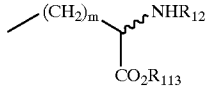
X is —$(CH_2)_n$—, O, S, NR_5, or $NC(O)R_6$ wherein n is an integer 0 or 1, R_5 is hydrogen, a C_1–C_4 alkyl, or an Ar—Y-group, and R_6 is —CF_3, C_1–C_{10} alkyl, or an Ar—Y-group;

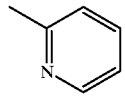
A_1 and A_2 are each independently hydrogen or —$COOR_7$ wherein R_7 is hydrogen, —CH_2O—$C(O)C(CH_3)_3$, a C_1–C_4 alkyl, an Ar—Y-group, or diphenylmethyl; with the proviso that where X is —$(CH_2)_n$— and A_1 is hydrogen then A_2 is —$COOR_7$, and where X is —$(CH_2)_n$— and A_1 is —$COOR_7$ then A_2 is hydrogen; and with the further proviso that where X is O, S, NR_5, or $NC(O)R_6$ then A_2 is hydrogen;

R_3 is hydrogen, C_1–C_8 alkyl, —$CH_2OCH_2CH_2OCH_3$ or an Ar—Y-group;

G is a radical chosen from the group;







wherein

m is an integer from 1 to 3;

R_8 is hydrogen, C_1–C_6 alkyl, —$CH_2CH_2S(O)_pCH_3$, or arylalkyl, wherein p is 0, 1, or 2;

R_9 is hydrogen, hydroxy, amino, C_1–C_6 alkyl, N-methylamino, N,N-dimethylamino, —CO_2R_7, or —$OC(O)R_{10}$ wherein R_{10} is hydrogen, C_1–C_6 alkyl, or phenyl;

R_{11} is 1 or 2 substituents independently chosen from the group consisting of; hydrogen, C_1–C_4 alkyl, C_1–C_4 alkoxy, or halogen;

R_{12} is hydrogen, C_1–C_6 alkyl, or Ar—Y-group;

R_{13} is hydrogen or C_1–C_4 alkyl;

V_1 is O, S, or NH;

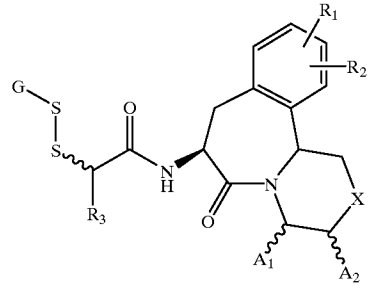
V_2 is N or CH;

V_3 is a direct bond or —C(O)—;

or stereoisomers or pharmaceutically acceptable salts thereof.

4. A method of treating hypertriglyceridemia in a patient in need thereof comprising administering to said patient a therapeutically effective hypertriglyceridemic amount of a compound of the Formula

Formula (I)



wherein

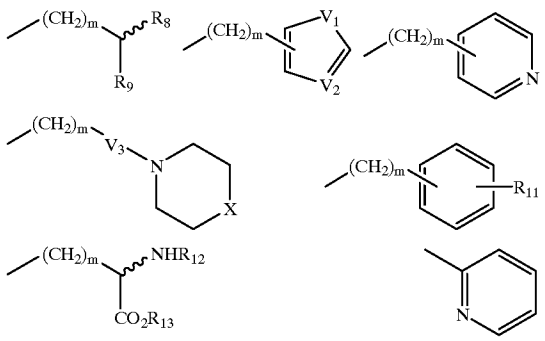
R_1 and R_2 are each independently hydrogen, hydroxy, —OR_4 wherein R_4 is a C_1–C_4 alkyl or an Ar—Y-group wherein Ar is aryl and Y is a C_0–C_4 alkyl; or, where R_1 and R_2 are attached to adjacent carbon atoms, R_1 and R_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

X is —$(CH_2)_n$—, O, S, NR_5, or $NC(O)R_6$ wherein n is an integer 0 or 1, R_5 is hydrogen, a C_1–C_4 alkyl, or an Ar—Y-group, and R_6 is —CF_3, C_1–C_{10} alkyl, or an Ar—Y-group;

A_1 and A_2 are each independently hydrogen or —$COOR_7$ wherein R_7 is hydrogen, —CH_2O—$C(O)C(CH_3)_3$, a C_1–C_4 alkyl, an Ar—Y-group, or diphenylmethyl; with the proviso that where X is —$(CH_2)_n$— and A_1 is hydrogen then A_2 is —$COOR_7$, and where X is —$(CH_2)_n$— and A_1 is —$COOR_7$ then A_2 is hydrogen; and with the further proviso that where X is O, S, NR_5, or $NC(O)R_6$ then A_2 is hydrogen;

R_3 is hydrogen, C_1–C_8 alkyl, —$CH_2OCH_2CH_2OCH_3$ or an Ar—Y-group;

G is a radical chosen from the group:



wherein

m is an integer from 1 to 3;

R_8 is hydrogen, C_1–C_6 alkyl, —CH_2—$CH_2S(O)_pCH_3$, or arylalkyl, wherein p is 0, 1, or 2;

R_9 is hydrogen, hydroxy, amino, C_1–C_6 alkyl, N-methylamino, N,N-dimethylamino, —CO_2R_7, or —$OC(O)R_{10}$ wherein R_{10} is hydrogen, C_1–C_6 alkyl, or phenyl;

R_{11} is 1 or 2 substituents independently chosen from the group consisting of hydrogen, C_1–C_4 alkyl, C_1–C_4 alkoxy, or halogen;

R_{12} is hydrogen, C_1–C_6 alkyl, or Ar—Y-group;

R_{13} is hydrogen or C_1–C_4 alkyl;

V_1 is O, S, or NH;

V_2 is N or CH;

V_3 is a direct bond or —C(O)—;

or stereoisomers or pharmaceutically acceptable salts thereof.

5. A method according to any of claims **1–4** wherein R_3 is phenylmethyl.

6. A method according to any of claims **1–4** wherein A_1 is —$COOR_7$ and A_2 is hydrogen.

7. A method according to any of claims **1–4** wherein A_1 is hydrogen and A_2 is hydrogen.

8. A method according to any of claims **1–4** wherein the compound is [7α(R*), 12bβ]-7-[(S)-(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

9. A method according to any of claims **1–4** wherein the compound is [7α(R*), 12bβ]-7-[(S)-(1-Oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine, (S)-1-(2-methylpropyl)-2-(thio)ethylamine, disulfide.

10. A method according to any of claims **1–4** wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

11. A method according to any of claims **1–4** wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, (S)-1-(2-methylpropyl)-2-(thio)-ethylamine, disulfide.

12. A method according to any of claims **1–4** wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, L-cysteine ethyl ester, disulfide.

13. A method according to any of claims **1–4** wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, benzylthio, disulfide.

14. A method according to any of claims **1–4** wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, ethylthio, disulfide.

15. A method according to any of claims **1–4** wherein the compound is [4S-[4α, 7α(R*), 12bS]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-hydroxyethylthio, disulfide.

16. A method according to any of claims **1–4** wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-pyridylmethylthio, disulfide.

17. A method according to any of claims **1–4** wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzazepine-4-carboxylic acid, 2-thioacetic acid morpholine carboxamide, disulfide.

* * * * *